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09/772,103	01/26/2001	Beatriz M. Carreno	GNN-009CP	7957

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Finnegan Henderson Farabow Garrett & Dunner LLP  
1300 I Street N W  
Washington, DC 20005-3315

EXAMINER

ROARK, JESSICA H

ART UNIT	PAPER NUMBER
1644	16

DATE MAILED: 11/22/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No.	Applicant(s)
	09/772,103	CARRENO ET AL.
	Examiner	Art Unit
	Jessica H. Roark	1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

1) Responsive to communication(s) filed on 16 September 2002.

2a) This action is **FINAL**.                    2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

4) Claim(s) 1-23 is/are pending in the application.

4a) Of the above claim(s) 16-23 is/are withdrawn from consideration.

5) Claim(s) \_\_\_\_\_ is/are allowed.

6) Claim(s) 1-15 is/are rejected.

7) Claim(s) \_\_\_\_\_ is/are objected to.

8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on 16 July 2001 is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on \_\_\_\_\_ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

#### Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some \* c) None of:

1. Certified copies of the priority documents have been received.

2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.

3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

#### Attachment(s)

1) Notice of References Cited (PTO-892)

2) Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6.

4) Interview Summary (PTO-413) Paper No(s) \_\_\_\_\_.

5) Notice of Informal Patent Application (PTO-152)

6) Other: \_\_\_\_\_.

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DETAILED ACTION

1. The Examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Jessica Roark, Art Unit 1644, Technology 1600.

2. Claims 1-23 are pending.

3. Applicant's election with traverse of Group I (claims 1-15) in Paper No. 11 (made final in Paper No. 12) and a species of calicheamicin in Paper No. 15 is acknowledged.

Applicant traverses the species election in Paper No. 15 on the grounds that a search can be conducted for the general concept of a toxic moiety.

In view of the art rejections set forth below, the species requirement is hereby WITHDRAWN.

Claims 16-23 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

*Claims 1-15 are under consideration in the instant application.*

4. Sequence compliance: The instant application appears to be in sequence compliance for patent applications containing nucleotide sequence and/or amino acid sequence disclosures.

5. Provisional application 60/178,473 appears to provide adequate written support for the instant claims.

6. Applicant's IDS, filed 1/2/02 (Paper No. 6), is acknowledged.

7. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

8. The disclosure stands objected to because of the following informalities: "Blanks" are present in the specification on pages 4, 5 and 28 for ATCC and hybridoma designations of the CTLA4 antibodies.

Applicant's request to hold correction in abeyance until such time as the ATCC designations can be provided is acknowledged.

Appropriate correction is required but held in abeyance.

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9. Claims 14 and 15 are objected to because of the following informalities: the claims recite "CLTA4" when it appears that -- CTLA4 -- was intended. Appropriate correction is required.

For examination purposes the claims will be interpreted to recite --CTLA4--.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

*The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.*

11. Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The following *written description* rejection is set forth herein.

Claim 1 recites that the antibody specifically recognizes "a molecule expressed only on activated T cells" as part of the invention.

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3<sup>rd</sup> column).

However, the specification appears to disclose only the molecule CTLA4 which is "a molecule expressed only on activated T cells". The specification does not appear to provide a disclosure of any particular structure that conveys an expression pattern limited to only activated T cells. The instant recitation requires no structural limitation with respect to the "molecule expressed only on activated T cells". Thus the instant recitation is essentially claiming in terms of a function (expression on a particular cell type) of the recited genus of molecules.

Consequently, Applicant was not in possession of the instant claimed invention. See Regents of the University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). Adequate written description of genetic material "requires a precise definition, such as by structure, formula, chemical name, or physical properties,' not a mere wish or plan for obtaining the claimed chemical invention." Id. 43 USPQ2d at 1404 (quoting Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606). The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter of the claim. Id. 43 USPQ2d at 1406. A description of what the genetic material does, rather than of what it is, does not suffice. Id.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant is invited to point to clear support or specific examples of the claimed invention in the specification as-filed.

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12. Claim 1 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody-toxic moiety conjugate comprising an antibody that specifically recognizes CTLA4 and certain other art-recognized molecules such as ACT-4/OX-40R; does not reasonably provide enablement for an antibody-toxic moiety conjugate comprising an antibody that specifically recognizes *any* "molecule expressed only on activated T cells". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized in *In re Wands* (8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and amount of experimentation required to enable one of skill in the art to practice the claimed invention.

There is insufficient guidance in the specification and a limited number of working examples such that one skilled in the art could practice the invention as broadly claimed. Although the specification discloses an antibody-toxic moiety conjugate comprising an antibody that specifically recognizes CTLA4, the specification provides insufficient guidance with respect to any other "molecule expressed only on activated T cells".

The identity of other molecules which meet this claim limitation is highly unpredictable. While certain other molecules were known in the art to be expressed only on activated T cells, such as the ACT-4/OX-40R (e.g., see U.S. Pat. No. 5,821332); the specification does not appear to provide sufficient guidance as to which other molecules are "expressed only on activated T cells". Neither does the specification appear to provide sufficient guidance as to how to identify other molecules expressed only on activated T cells. It would require undue experimentation of the skilled artisan to identify other molecules meeting this claim limitation, prepare antibodies to the molecules, and then provide an antibody-toxic moiety conjugates comprising the antibodies.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. In view of the insufficient guidance in the specification and limited number of working examples; the experimentation left to those skilled in the art to make the instantly recited antibody-toxic moiety conjugates as broadly recited, is unnecessarily, and improperly, extensive and undue.

13. Claims 14 and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a humanized antibody that is specifically reactive with human CTLA4 wherein the antibody comprises *the* amino acid sequence of SEQ ID NO:8 and the amino acid sequence of SEQ ID NO:10 or a humanized antibody that comprised the subsequences of SEQ ID NOS:8 and 10 (or SEQ ID NOS:6 and 4) that correspond to *all six complementarity determining regions* (CDRs), does not reasonably provide enablement for a humanized antibody comprising non-CDR subsequences (i.e., "an amino acid sequence as shown.."), or comprising only a light chain (claim 14) or only a heavy chain (claim 15) sequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

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The claims recite an humanized antibody reactive with human CTLA4 that comprises “*an* amino acid sequence as shown in SEQ ID NO:8” (claim 14) *or* “*an* amino acid sequence as shown in SEQ ID NO:10” (claim 15) as part of the invention.

The specification discloses that *a combination* of subsequences of SEQ ID NO:8 and SEQ ID NO:10 *that correspond to the complementarity determining regions* (CDRs) are essential to provide the recited function of reactivity with human CTLA4. However, the scope of instant claims 14 and 15 encompasses a genus of antibodies comprising *any* subsequence of *either* SEQ ID NO:8 *or* SEQ ID NO:10. Applicant does not appear to have provided sufficient guidance as to which other non-CDR subsequences of SEQ ID NOS:8 and 10 can be utilized to make an antibody which reacts with human CTLA4. Further, Applicant does not appear to have provided sufficient guidance as to which other heavy (claim 14) or light (claim 15) chains would pair with the recited light (claim 14) or heavy (claim 15) chains to produce an antibody that was reactive with human CTLA4, other than an antibody which comprises both the light chain of SEQ ID NO:8 and the heavy chain of SEQ ID NO:10.

The state of the art recognized that the only subsequences which could be derived from an antibody and still convey antigen reactivity were a combination of all three CDRs of the heavy chain variable region and all three CDRs of the light chain variable in the context of an antibody framework. For example, Bendig (Methods: A Companion to Methods in Enzymology 1995; 8:83-93) reviews that the general strategy for “humanizing” antibodies involves the substitution of all six CDRs from a rodent antibody that binds an antigen of interest, and that all six CDRs are involved in antigen binding (see entire document, but especially Figures 1-3). The specification does not appear to provide any working examples which contradict this minimal structural requirement.

Therefore, it would be highly unpredictable that a humanized antibody comprising subsequences (i.e., those sequences encompassed by the use of the indefinite article “*an*” in the phrase “*an* amino acid sequence shown in..” of an antibody light chain variable region (claim 14) or heavy chain variable region (claim 15), would bind the same antigen as the parental antibody. Thus the minimal structure which the skilled artisan would consider predictive of the function of reactivity with human CTLA4 includes six CDRs (three in the heavy chain variable region and three in the light chain variable region) from the same parental antibody in the context of an antibody framework.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Given the recognized unpredictable nature of making antibodies with a desired specificity having fewer than all six CDRs (three from the heavy and three from the light chain) of a reference antibody and the lack of sufficient guidance provided in the specification; the experimentation left to those skilled in the art, is unnecessarily, and improperly, extensive and undue.

It is noted that a claim limited to a recitation of “a humanized antibody that is specifically reactive with human CTLA4, wherein the antibody comprises *the* light chain amino acid sequence set forth in SEQ ID NO:8 and *the* heavy chain amino acid sequence set forth in SEQ ID NO:10” would obviate this rejection.

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14. With respect to claim 12, it is noted that if the claim is amended to include ATCC Deposit information, then the hybridomas would be required to practice the claimed invention., The enablement requirements of 35 U.S.C. 112, first paragraph, may be satisfied by a deposit of the pertinent hybridomas. See 37 CFR 1.801-1.809.

Applicant is reminded of the following with respect to Deposit Practice:

*In addition to the conditions under the Budapest Treaty, Applicant is required to assure that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications* (see 37 CFR 1.808 (a)(2) and MPEP 2410-2410.01).

Amendment of the specification to disclose the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, Applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

NOTE THE CURRENT ATCC DEPOSITORY ADDRESS:

American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209.

*If the original deposit is made after the effective filing date of an application for patent, Applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state that the biological material which is deposited is the biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which case the statement need not be verified. See 37 CFR 1.804(b) and MPEP 2406.*

15. The following is a quotation of the second paragraph of 35 U.S.C. 112.

*The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.*

16. Claims 7 and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 7 is indefinite in its recitation of "modulating" because it is ambiguous as to the direction (positive or negative) or degree of said modulating.

B) Claim 12 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite. Because there are "blanks" in the claim, the claim fails to point out what is included or excluded by the claim language.

Applicant's comments in Paper No. 15 are acknowledged. However, until such time as the claim is either cancelled or amended to provided the missing deposit numbers, the rejection is appropriate.

C) Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

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17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

*(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.*

18. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Godfrey et al. (U.S. Pat. No. 5,821,332, issued 10/13/1998, see entire document).

Godfrey et al. teach the human polypeptide ACT-4 and that this receptor is expressed only on the surface of activated CD4 T cells, its expression being absent on resting T cells as well as on other cell types in physiological conditions (see entire document, but especially columns 9-10 and in particular column 10 at lines 11-17).

Godfrey et al. also teach antibodies to the human ACT-4 protein, including monoclonal antibodies (see especially columns 14-18).

Godfrey et al. teach that the anti-ACT-4 antibodies can be conjugated to a toxic moiety for use as an immunotoxin (see especially the bridging paragraph of column 17-18). Godfrey et al. teach that there are many suitable toxin components (column 18 at lines 6-11), including the bacterial toxin ricin (column 18 at lines 6-11 in view of column 10 at lines 47-49).

The reference teachings thus anticipate the instant claimed invention.

19. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

*(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

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20. Claims 1-7, 10-11 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Godfrey et al. (U.S. Pat. No. 5,821,332) and Kuchroo et al. (U.S. Pat. No. 6,207,156).

The claims are drawn to an antibody-toxic moiety conjugate comprising a humanized monoclonal antibody that specifically recognizes human CTLA4, including wherein the antibody blocks binding of CTLA4 to CD80 or CD86.

Godfrey et al. teach the human polypeptide ACT-4 and that this receptor is expressed only on the surface of activated CD4 T cells, its expression being absent on resting T cells as well as on other cell types in physiological conditions (see entire document, but especially columns 9-10 and in particular column 10 at lines 11-17).

Godfrey et al. also teach antibodies to the human ACT-4 protein, including monoclonal antibodies and humanized monoclonal antibodies (see especially columns 14-18).

Godfrey et al. teach that the anti-ACT-4 antibodies can be conjugated to a toxic moiety for use as an immunotoxin (see especially the bridging paragraph of column 17-18). Godfrey et al. teach that there are many suitable toxin components (column 18 at lines 6-11), including the bacterial toxin ricin (column 18 at lines 6-11 in view of column 10 at lines 47-49).

Godfrey et al. teach that immunotoxins comprising anti-ACT-4 antibodies, including humanized anti-ACT-4 antibodies, can be used as therapeutic reagents to suppress undesired immune responses by selectively eliminating activated CD4 T cells (see entire document, but especially column 22 at lines 11-36). Godfrey et al. teach that therapeutic agents which selectively eliminate activated cells are particularly advantageous because such reagents eliminate the cells involved in the undesired immune response while sparing non-activated T cells and preserving a residual immune capacity (see comments at column 22 lines 27-36).

Godfrey et al. review in column 2 the art-recognized motivation for developing multiple reagents which targeted different cell-surface receptors for use in methods of suppressing undesired immune responses. In particular, Godfrey et al. note that when using a single therapeutic agent to suppress an undesired immune response in a patient the patient may develop an immune response to the agent which prevents its effect and that cells expressing the target antigen may adapt to the therapy by ceasing to express the target antigen.

Finally, Godfrey et al. also note that the art recognized that while it was desirable to develop multiple reagents, the ideal reagents block only undesired immune responses while leaving a residual capacity to effect desirable immune responses (see especially comments at column 2, lines 7-40).

Kuchroo et al. teach monoclonal antibodies to human CTLA4 which bind to CTLA4 and prevent the interaction of B7 with human CTLA4 (see entire document, e.g., "Summary of the Invention" at columns 2-4). Kuchroo et al. teach that the anti-human CTLA4 monoclonal antibodies may be humanized (e.g., column 2 at lines 48-60 and columns 7-9). Kuchroo et al. review that CTLA4 is a molecule expressed only on activated T cells (see comment at column 1, lines 60-67). Kuchroo et al. further review that "B7" includes B7-1 and B7-2 (e.g., column 1 at lines 27-50). B7-1 is an alternate name for CD80 and B7-2 is an alternate name for CD86.

Kuchroo et al. do not teach an antibody-toxic moiety conjugate comprising a humanized monoclonal antibody that specifically recognizes human CTLA4, including wherein the antibody blocks binding of CTLA4 to CD80 or CD86.

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However, given the teachings of Godfrey et al. that it was desirable to produce toxins conjugated to different antibodies which each targeted different cell surface molecules expressed selectively on cells involved in undesired immune responses in order to eliminate the cells *in vivo* and the teachings of Kuchroo et al. of antibodies to the CTLA4 antigen expressed on activated T cells; it would have been obvious to the ordinary artisan at the time the invention was made to produce antibody-toxin moiety conjugates comprising the anti-CTLA4 antibodies of Kuchroo et al. As noted *supra*, Godfrey et al. teach that many different toxins are suitable for conjugating to antibodies, and points in particular to the bacterial product ricin (column 18 at lines 6-11). As also noted *supra*, the antibodies of Kuchroo et al. prevent the interaction of B7 with human CTLA4 (see entire document, e.g., "Summary of the Invention" at columns 2-4). In addition, the antibodies of Kuchroo, because they do prevent the interaction of B7 with human CTLA4 would also necessarily bind to a region of the CTLA4 molecule in spatial proximity to the site of CTLA4 binding to a costimulatory molecule. Similarly, binding of the antibodies of Kuchroo et al. would necessarily be modulated by a substitution in CTLA4 at position 83 of SEQ ID NO:2. The ordinary artisan would have had a reasonable expectation of producing the instant antibody-toxic moiety conjugate given the availability of the anti-CTLA4 antibodies of Kuchroo et al. and the standardized techniques for conjugating any of a variety of toxic moieties to an antibody. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

21. Claims 8-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Godfrey et al. (U.S. Pat. No. 5,821,332) and Kuchroo et al. (U.S. Pat. No. 6,207,156) as applied to claims 1-7, 10-11 and 13 above, and further in view of Hamann et al. (U.S. Pat. No. 5,773,001).

The claims are drawn to an antibody-toxic moiety conjugate comprising an antibody that specifically recognizes CTLA4 and a toxic moiety that is the carbohydrate calicheamicin.

Godfrey et al. and Kuchroo et al. have been discussed *supra*.

Godfrey et al. and Kuchroo et al. do not teach an antibody-toxic moiety conjugate comprising carbohydrate calicheamicin.

However, as noted *supra*, Godfrey et al. teach that any of a number of toxins are suitable components of an antibody-toxic moiety conjugate (column 18 at lines 6-11).

Hamann et al. teach that calicheamicin is a potent toxin that can be conjugated to antibodies, including humanized antibodies, and used to eliminate cells expressing the antigen recognized by the antibody of the conjugate (see entire document, especially "Background of the Invention" at columns 6-20).

It would therefore have been obvious to the ordinary artisan at the time the invention was made to substitute the carbohydrate calicheamicin for the toxin moiety of the antibody-toxin immunoconjugate taught by Godfrey et al. and Kuchroo et al. The ordinary artisan would have been motivated to make such a substitution in view of the recognized suitability of calicheamicin in antibody-toxin conjugates, and because Hamann et al. teach that calicheamicin is a potent toxin. Given the teaching of antibody-calicheamicin conjugates by Hamann et al., the ordinary artisan would have had a reasonable expectation that the antibodies of Kuchroo et al. could also be conjugated to calicheamicin to produce antibody-toxic moiety conjugate comprising an antibody that specifically recognizes CTLA4 and a toxic moiety that is the carbohydrate calicheamicin. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

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22. No claim is allowed.

23. The full length sequences of SEQ ID NO:8 and SEQ ID NO:10 appear to be free of the prior art.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica H. Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday, 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Jessica Roark, Ph.D.  
Patent Examiner  
Technology Center 1600  
November 20, 2002

PHILLIP GAMBEL  
PRIMARY EXAMINER  
TECH CENTER 1600  
11/20/02